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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,312	06/05/2006	Sung Youb Jung	430156.404USPC	5682

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/04/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

sughrue@sughrue.com
PPROCESSING@SUGHRUE.COM
USPTO@SUGHRUE.COM

Office Action Summary	Application No.	Applicant(s)	
	10/535,312	JUNG ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9,11-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,11, 12 and 16* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/09* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6, 8, 9, 11-13, 15 and 16 are all the pending claims for this application.

2. Claim 7 was cancelled and Claims 1-3, 6, 8, 13 and 16 were amended in the Response of 8/31/09.

3. Claim 15 is withdrawn from examination.

4. Claims 1-6, 8, 9, 11-13 and 16 are all the pending claims under examination.

5. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

Information Disclosure Statement

6. The IDS of 10/9/09 has been considered and entered. The initialed and signed 1449 form is attached.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

7. The rejection of Claims 1-9, 11, 12, and 16 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for any Ig constant regions that are just any combinations and any hybrids of IgG, IgA, IgM, IgE, and IgD, *or* just any combinations and any hybrids of IgG1, IgG2, IgG3, IgG4 or CH1, CH2, CH3, CH4 and CL is withdrawn.

Applicants' have amended the claims to delete the limitations for "combinations and hybrids thereof" for the Ig constant regions and have drawn to invention to an Ig constant region encompassing CH1, hinge, CH2, CH3 and/or CH4. Applicants comments on pp. 5-6 of the Response of 8/13/09 are acknowledged.

Claim Rejections - 35 USC § 103

8. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) is withdrawn.

Applicants' have amended the claims to introduce the limitation for the nucleotide encoding an Ig constant region without a variable region and which distinguishes the method from Capon and Reilly. Applicants' comments on pp. 6-10 of the Response of 8/13/09 are acknowledged.

9. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) as applied to claims 1 and 11 above, and further in view of Kwon et al. (USPN 6605697; published 8/12/03; filed 6/14/01) is withdrawn.

Applicants' have amended the claims to introduce the limitation for the nucleotide encoding an Ig constant region without a variable region (e.g., Fc) and which

distinguishes the method from Capon and Reilly. Applicants' comments on pp. 6-10 of the Response of 8/13/09 are acknowledged.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1-6, 8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09).

Claims 1-6, 8 and 16 are interpreted as being drawn to a method for producing a Ig Fc in the cytoplasm or secreted from an E coli having been transfected with a nucleotide encoding the STII signal sequence and the Ig Fc domain without a variable

domain (Claim 1), where the Ig Fc region is from IgG, IgA, IgM, IgE or IgD, (Claim 2) or for the subtypes IgG1, IgG2, IgG3 and IgG4 (Claim 3), or IgG4 (Claim 4), where the Fc of Claim 4 is aglycosylated (Claim 5), and Fc comprises a portion of a hinge (Claim 6 and 16), and where the Fc is from a heavy or light chain (Claim 8).

It would have been prima facie obvious to have produced the instant claimed method for producing soluble Ig Fc domains from an E. coli in view of Kitai, Simmons and Sytkowski.

Kitai discloses a penicillinase signal peptide and hIgG-Fc were fused through the one additional amino acid, Ser. This hybrid protein was translocated "across the inner membrane, correctly processed between Ala and Set, and excreted into the culture medium in the dimeric form. These results indicate that this penicillinase signal peptide works efficiently, even when a foreign protein is fused. Kitai discloses plasmid pEAP8 was an excretion vector in *E. coli* transformants (Kate e tal. 1987) and containing the DNA region needed for the extracellular production in E. coli, that is Kll gene of pMB9, Ex promoter.and penicillinase promoter-signal-peptide. Kitai does not teach using the heat-stable enterotoxin signal peptide or the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas do Simmons and Sytkowski.

Simmons discloses examples of three heat stable enterotoxin (STII) signal sequence derivatives differing only in the TIR and maintaining the wildtype amino acid sequence (Table 1, variants 1, 4, 6) which improved the secretion of a sample of heterologous proteins over wildtype STII constructs in *E coli* transformants. Simmons compared expression of a heterologous gene of interest inserted downstream of the

phoA promoter, trp Shine-Delgarno and an STII signal sequence possessing a different relative TIR strength. Simmons teaches the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor. Simmons appreciates producing heterologous proteins using the STII signal sequence but does not suggest the heterologous protein is the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas does Sytkowski. The IgG of Kitai would also be considered a heterologous protein with respect to the E. coli host expression system.

Sytkowski teaches cloning Fc domains from IgGl, IgG2, IgG2a, IgG3, IgG4, IgM, IgA, IgD or IgE of the heavy or light chain, where the Ig constant region comprises immunoglobulin hinge region, CH2 domain and CH3 domain or CL1 domain, respectively. Sytkowski teaches the entire immunoglobulin heavy chain constant region (CHI-hinge-CH2-CH3) or alternatively, the immunoglobulin constant region can comprise all, or a portion of the hinge region, the CH2 domain and the CH3 domain. The immunoglobulin constant region can also comprise the CL1 domain of an immunoglobulin light chain. Finally Simmons teaches a fusion protein may comprise a signal or targeting sequence (p. 5). The proteins of Sytkowski use the cloned Fc domains to create a fusion protein with cloned EPO, however, it is the examiner's position that the EPO portion is not important or essential and can be removed from the Sytkowski art reference method in setting forth this obviousness rejection, see Eisai Co. v. Dr. Reddy's Laboratories, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (noting in regard to

obviousness, that the record provided no reason to start with a lead compound and then drop the feature of the lead compound that leads to its advantageous properties) (cited at page 3 of the Reply Br.). The ordinary artisan would not have considered the EPO portion an essential element, such that its removal would render the method of Sytkowski inoperable. This is supported by the implied statements of Sytkowski that the Ig constant domain alone binds the Fc receptor or can have ADCC or ACC activity or extends the half-life of a molecule to which it is attached (p. 15), and thus to produce an isolated Fc would have advantages for other uses other than fusing it to EPO.

The ordinary artisan would have been motivated and reasonably assured of success in having produced the instant claimed method in view of Kitai, Simmons and Sytkowski. The references alone address the expression of cloned proteins in E. coli systems where Kitai and Simmons use different but otherwise interchangeable signal sequences and replacing the penicillinase sequence with the STII sequence of Simmons would seemingly improve the product outcome in E. coli cytosol as well as secreted proteins. To have considered expressing an Fc protein was contemplated and reduced to practice by Kitai and therefore obvious, and further where Simmons appreciates using the STII to express many different heterologous proteins in E. coli, where contiguous or portions of Fc domains including portions of the hinge from different antibody isotypes and isoforms were contemplated by Sytkowski in a fusion protein format. The ordinary artisan would have appreciated that human proteins expressed in E. coli would not be glycosylated, so that an Fc from IgG4 would have been aglycosylated using the claimed method. The ordinary artisan would have been

assured of success because the level of skill and technology and the reagents for producing isolated Fc's was already reduced to practice as set forth in the three references where in order to obtain an abundance of purified Fc proteins absent further manipulation than fusing the Fc to an STII sequence, the ordinary artisan could have predicted a reasonably achievable outcome.

11. Claims 1, 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Lilly (US 20040053370; filed 5/29/03).

The interpretation of Claim 1 is discussed above under section 10. Claims 9 and 12 are drawn to the Fc isotype for IgG4 of SEQ ID NO:29.

Lilly teaches an Fc sequence having 100% identity to SEQ ID NO 29 of Claims 9 and 12 (see attached sequence search alignment) and used to construct fusion proteins. Lilly teaches "[0238] Based on these studies, Fc regions can be modified at the catabolic site to optimize the half-life of the fusion proteins. It is preferable that the Fc region…be derived from an IgG1 or an IgG4 Fc region…and even more preferable that the Fc region be IgG4or derived from IgG4. Preferably the IgG Fc region contains both the CH2 and CH3 regions including the hinge region. Thus in view of Kitai, Simmons and Sytkowski, the ordinary artisan would have found motivation use the IgG4

Fc of Lilly in the construct of Kitai in view of Simmons and Sytkowski where according to Lilly the IgG4 Fc is preferable.

12. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Kwon et al. (WO200015661; published 3/23/00).

The interpretation of Claim 1 is discussed above under section 10. Claim 11 is drawn to the heat stable enterotxin signal sequence of SEQ ID NO: 36, 37, 38, 40, 41, 42, 43, 44, 45, or 46.

Kwon teaches heat stable enterotoxin II signal sequence having 100% identity to SEQ ID NO: 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46 of Claim 11 (see attached sequence search alignments) and used to construct fusion proteins. Kwon teaches the modified signal sequences enhance the efficiency of peptide secretion from the E. coli cells, and the modified signal peptides may be used according to standard recombinant DNA methodolgies to direct the secretion of peptides from microorganisms (Abstract). Thus in view of Kitai, Simmons and Sytkowski, the ordinary artisan would have found motivation to use the modified signal peptide sequences of Kwon in the construct of Kitai in view of Simmons and Sytkowski where the ordinary artisan would be reasonably assured that the signal peptides would have enhanced the secretion of Fc.

Conclusion

13. No claims are allowed.

14. Claims 13 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 10/9/09 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643